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PROTOCOL

ExplorinG frailty and mild cognitive impairmEnt in kidney tRansplantation to predict biomedicAl, psychosocial and health cost outcomeS (GERAS): protocol of a nationwide prospective cohort study

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See Appendix 1.

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Abstract

Aim. To present the rationale, design and methodology of the GERAS project, which examines whether assessment of frailty and mild cognitive impairment could enhance risk prediction for biomedical, psychosocial outcomes and foster efficient resource allocation in kidney transplantation.

Background. For the burgeoning cohort of older patients considered for kidney transplantation, evidence gaps regarding frailty and mild cognitive impairment limit clinical decision-making and medical management. As known risk factors for 'hard' clinical outcomes in chronic illness, both require further study in transplantation. Integrating these and other bio-psychosocial factors into a comprehensive pre-transplant patient assessment will provide insights regarding economic implications and may improve risk prediction.

Design. A nation-wide multi-centre prospective cohort study nested in the Swiss Transplant Cohort Study.

Methods. Our nationally representative convenience sample includes 250 adult kidney transplant recipients. Data sources include the Swiss Transplant Cohort Study and primary data collected at time of transplantation, 6 months, 1 and 2 years post-transplant via established measures (the Montreal Cognitive Assessment, Psychosocial Questionnaire, Fried Frailty Instrument and a blood analysis), investigator-developed instruments and datasets compiled by hospitals' management control units, sickness funds, the Swiss Federal Statistical Office and the European Renal Association.

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Descriptive, competing risk survival and mixed effects analyses will be performed. Research Ethics Committee approval was obtained in January 2016.
Discussion. This pioneering project jointly examines frailty and mild cognitive impairment from bio-psychosocial and health economic perspectives. Results may significantly inform risk prediction, care tailoring and resource optimization to improve health outcomes in the ageing kidney transplant cohort.

Keywords: frailty, health economics, kidney transplantation, midwives, mild cognitive impairment, nurses, nursing, older patients, risk prediction, multi-centre prospective cohort study

Why is this study or review needed?

- Despite rising numbers of older adults being evaluated for and undergoing kidney transplantation, there is a lack of evidence to guide risk prediction for this cohort.
- Preliminary evidence indicates that frailty and mild cognitive impairment are highly prevalent and are independent predictors of adverse biomedical outcomes in kidney transplantation
- The GERAS study is the first to examine frailty and mild cognitive impairment from a comprehensive bio-psychosocial and health economic perspective. It will provide evidence for healthcare professionals to better identify patients most at risk for adverse outcomes. This can guide early intervention and tailor pre- and posttransplant care, policy development and resource allocation, aiming to improve outcomes for the growing cohort of elderly and frail kidney transplant recipients

Introduction

Increasing numbers of older patients with end-stage renal disease (ESRD) are receiving kidney transplants (Abecassis *et al.* 2012, Goldstein 2012, McAdams-Demarco *et al.* 2013a). Even in countries where age directly limits graft access, kidney transplantation (KTx) populations are greying (European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), 2013, United Network for Organ Sharing (UNOS) - Organ Procurement and Transplantation Network (OPTN), 2014a). Older patients' medical needs, however, present major challenges for the KTx healthcare agenda, as there is limited evidence to guide clinical decision-making for organ allocation, and pre- and posttransplant management in this cohort. Therefore, exploring outcome-predictive factors in older KTx patients is a rapidly rising research priority (Abecassis *et al.* 2012, Goldstein 2012, Singh *et al.* 2016). In Switzerland, where chronological age is not a listing criterion for kidney transplantation, over one-fifth (ca. 22·5%) of recipients are aged ≥65 years at time of transplantation (Tx) (Koller *et al.* 2014). This gives Swiss transplant centres broad opportunities to study this older cohort's outcomes.

Background

Frailty as a risk prediction criterion for older KTx patients

Growing evidence suggests that, independent of chronological age and comorbidities, frailty can guide risk prediction in chronically ill patient groups (Makary *et al.* 2010, Flint *et al.* 2012, Hamaker *et al.* 2012, Partridge *et al.* 2012, Dunlay *et al.* 2014, Lai *et al.* 2014a, Jha *et al.* 2015, Musso *et al.* 2015, Robinson *et al.* 2015, Singer *et al.* 2015). While frailty and comorbidities frequently co-exist, they are distinct conditions with independent predictive values regarding adverse outcomes (Fried *et al.* 2004, Danon-Hersch *et al.* 2012, Clegg *et al.* 2013, Chen *et al.* 2014). Comorbidity is the simultaneous or sequential occurrence and interaction of two or more disorders in the same patient; frailty is a cumulative functional decline across physiological systems, limiting the body's resilience against stressors. For example, responding to surgical procedures, immunosuppressive medications, or infections, frail patients experience disproportional deterioration in health status and adverse outcomes (Fried *et al.* 2001, Clegg *et al.* 2013, Chen *et al.* 2014). Preliminary findings from longitudinal studies using the Fried Frailty Phenotype (Fried *et al.* 2001) indicate that frail and pre-frail patients with ESRD and solid organ Tx recipients have inferior clinical outcomes, for exampl, higher rates of dialysis re-initiation, early hospital readmission and posttransplant mortality.

While KTx-specific links between frailty and such outcomes is based on a single US patient cohort (Garonzik-Wang *et al.* 2012, Roshanravan *et al.* 2012, Johansen *et al.* 2013, McAdams-Demarco *et al.* 2013a,b, 2015b, Exterkate *et al.* 2016, Lam & Jassal 2015, Musso *et al.* 2015, Singer *et al.* 2015, Jha *et al.* 2016a, Wilson *et al.* 2016), these findings are extremely relevant: up to 42% and 29% of adult haemodialysis patients are respectively pre-frail or frail (Johansen *et al.* 2013, Musso *et al.* 2015); and respectively 25% and 33% of adult KTx recipients present with frailty or pre-frailty (Garonzik-Wang *et al.* 2012, McAdams-Demarco *et al.* 2013a,b, 2015b).

Importantly, as frailty also occurs in younger adults with ESRD and accelerated metabolic ageing (Kooman *et al.* 2014, Musso *et al.* 2015), it is relevant across age groups. In 2016, the International Society for Heart and Lung Transplantation became the first international Tx body to integrate frailty into its heart Tx listing criteria (Comans *et al.* 2016). Still, while the American College of Surgeons has published guidance to integrate frailty assessments into the care of older surgical patients (Robinson *et al.* 2015), no clinical practice guidelines yet exist to integrate frailty assessment into KTx care.

Frailty in KTx: applying a bio-psychosocial perspective and studying mild cognitive impairment (MCI)

Interplay between biomedical, psychosocial and behavioural factors determines Tx patients' risks regarding adverse outcomes. Psychosocial factors also independently predict poor posttransplant outcomes (Denhaerynck *et al.* 2005, Mehra *et al.* 2006, Dobbels *et al.* 2008, Gordon *et al.* 2009, Pinsky *et al.* 2009, Garg *et al.* 2012, De Geest *et al.* 2013, 2014, Pascual *et al.* 2014). In addition, as patient-reported outcomes, for example, health-related quality of life (HR-QOL), are increasingly valued in KTx research (Molnar-Varga *et al.* 2011, De Geest *et al.* 2013, Kumnig *et al.* 2014, Seiler *et al.* 2015), comprehensive bio-psychosocial pre-Tx evaluations are endorsed by international Tx societies and included in KTx clinical management guidelines (Sharing) (Mehra *et al.* 2006, Pascual *et al.* 2014).

While pre-frailty and frailty are consistently associated with poorer HR-QOL in non-Tx populations (Kojima *et al.* 2016), frailty studies in Tx have thus far accounted mainly for biomedical Tx risk factors (McAdams-Demarco *et al.* 2013a,b, 2015b, Singer *et al.* 2015). As a predictor of HR-QOL, only one study has compared frailty with liver disease severity (Derck *et al.* 2015). To examine how frailty data can improve bio-psychosocial risk prediction in KTx, prospective pre- to post-Tx studies are essential.

Furthermore, emerging evidence links frailty with MCI, a measurable decline in cognitive function that is excessive relative to a patient's chronological age and educational background but allows basic daily life activities (Apostolo *et al.* 2015) (Auyeung *et al.* 2011, Yassuda *et al.* 2012, Kelaiditi *et al.* 2013, Halil *et al.* 2015, Jha *et al.* 2016a). Up to 55·0% of adult ESRD patients exhibit MCI, which independently predicts hospital readmissions and mortality in older adults (Auyeung *et al.* 2011, Drame *et al.* 2011, Jacobs *et al.* 2011, Cano *et al.* 2012, Yassuda *et al.* 2012). Although cognitive deficits primarily improve posttransplant, they may also persist (Griva *et al.* 2006, Van Sandwijk *et al.* 2015, Dixon *et al.* 2016). Recently, MCI was linked with frailty in haemodialysis patients (McAdams-Demarco *et al.* 2015c); and in end-stage heart failure, assessing MCI alongside frailty improved mortality prediction (Jha *et al.* 2016b). Joint examinations of frailty and MCI in KTx are needed to clarify their interrelationships and synergistic predictivity regarding negative outcomes.

Frailty and MCI in KTx: the need for a health economic perspective

While dialysis and KTx are both extremely costly, KTx is clearly more cost-effective (Ferguson *et al.* 2015, Sanchez-Escuredo *et al.* 2015). However, as KTx demands

significantly exceed graft availability, fair allocation demands risk prediction models that predict both personal and societal costs. Through reliable analyses of resources used and health outcomes, health economic analyses can optimize healthcare resource allocation (Wong *et al.* 2014, Drummond *et al.* 2015, Ferguson *et al.* 2015, Sanchez-Escuredo *et al.* 2015). As frailty is a long-term condition with adverse patient and healthcare system outcomes, frail, and pre-frail older non-institutionalized patients use more healthcare resources than their non-frail counterparts (Sirven & Rapp 2014, Harrison *et al.* 2015, Ilinca & Calciolari 2015, Lyndon 2015). However, the impacts of frailty and MCI on healthcare and societal costs and on quality-adjusted life years (QUALYs) remains unexplored in KTx. The GERAS study will provide essential evidence for further studies on how frailty and MCI influence KTx costs.

Advancing frailty and MCI research in KTx by examining the conditions' development and aetiology

While frailty can improve, without intervention, older non-Tx patients' frailty commonly worsens (Clegg *et al.* 2013, Apostolo *et al.* 2015, Goldraich *et al.* 2015, Harrison *et al.* 2015, Musso *et al.* 2015). Nevertheless, in KTx, the one available study examining frailty changes indicates immediate posttransplant deterioration, with recovery to baseline status or better after 3 months (McAdams-Demarco *et al.* 2015a). Longitudinal post kidney transplantation cognitive function studies are rare. While two studies have reported net posttransplant improvements, their results have limited applicability to older patients, as both included relatively young patients (Griva *et al.* 2006, Van Sandwijk *et al.* 2015). Research with extended follow-up times and across adult KTx recipients of all ages will provide key insights into frailty's pre-Tx to posttransplant development.

Concomitantly, current biological frameworks of frailty aetiology (see 'conceptual frameworks') suggest origins in the dysregulation of the neuroendocrine, musculoskeletal, metabolic and other physiological systems (Fulop *et al.* 2015). In older non-Tx cohorts, recent longitudinal studies suggest the immune/inflammatory system as a key pathway (Leng *et al.* 2007, 2009, Li *et al.* 2011, Collerton *et al.* 2012, Chen *et al.* 2014). Complex immune system alterations are hypothesized to cause chronic low-grade systemic inflammation, inducing frailty and increasing susceptibility to chronic conditions, disabilities and mortality (Fulop *et al.* 2015). Associations between frailty and certain pro-inflammatory markers – interleukin-6 (IL-6), tumour necrosis factor α (TNF-α) and C-reactive protein (CRP) and white blood cell count (WBC) – are well-documented (Leng *et al.* 2007, 2009, Li *et al.* 2011, Collerton *et al.* 2012, Chen *et al.* 2014, Theou & Rockwood 2015). Notably, despite emerging aetiological pathways for MCI (Halil *et al.* 2015), no reliable causal relationship has been established (Gale *et al.* 2013, Fulop *et al.* 2015, Theou & Rockwood 2015). With only one related study in Tx recipients (Singer *et al.* 2015), inflammation markers' pre-Tx to post-transplant evolution and their interrelationships with frailty and MCI in KTx offer high research potential (De Martinis *et al.* 2006, Li *et al.* 2011, Gale *et al.* 2013, Fulop *et al.* 2015, Hubbard & Jatoi 2015).

The study

Aims

The GERAS study's primary aims are: (1.1) to examine whether pre-Tx frailty and MCI predict patient's survival and HR-QOL posttransplant (primary outcome) and graft survival and acute rejection episodes (secondary outcomes); (1.2) to explore whether pre-Tx frailty and MCI predict healthcare and societal costs of KTx; and (1.3) to assess and compare posttransplant QUALYs of KTx recipients who are non-frail, pre-frail/frail and pre-frail/frail with MCI. Our initial hypothesis is that pre-Tx frailty and MCI can have a negative impact on these primary and secondary outcomes.

The project's secondary aims are: (2.1) to examine the prevalence, evolution and interrelationships of frailty and MCI for 2 years posttransplant; (2.2) to examine the levels of selected inflammatory biomarkers (CRP, total WBC, TNF-α and IL-6) in relationship with frailty status and MCI; and (2.3) to explore whether pre-Tx levels of the selected biomarkers predict changes in frailty status and cognitive function.

Methodology

Conceptual frameworks

The GERAS study employs four conceptual frameworks: (1) The Fried Frailty Phenotype is an internationally applied, psychometrically validated conceptual model of frailty. Based on indicators of physical fitness and metabolism, it measures weakness, slowness, low levels of physical activity, lower total energy expenditure and chronic undernutrition. Depending on the number of indicators present, patients are classed as: non-frail (score 0); pre-frail (score 1-2); or frail (score ≥3) (Fried *et al.* 2001, 2004, Cesari *et al.* 2014, Walston & Bandeen-Roche 2015). This is predominantly applied in end-stage organ failure to predict risks of adverse outcomes independent of chronological age, comorbidities and disabilities. Its 10-

minute administration time suits it to routine clinical application (Exterkate *et al.* 2016). (2) The STCS-developed Expanded Biopsychosocial Framework for Transplant Research (described by De Geest *et al.* 2013) provides biopsychosocial perspective to select outcomes and confounders. (3) Chen *et al.*'s (2014) conceptual model will guide explorations of the interrelationships between frailty and MCI and (4) Halil *et al.*'s (2015) model highlights chronic low-grade systemic inflammation's aetiological role in both conditions.

Study design, setting

GERAS is a multi-centre prospective cohort study across five Swiss KTx centres. It is nested in the STCS, a long-term open prospective cohort study that has enrolled over 95% of KTx recipients in Switzerland since 2008. More information on the STCS is described elsewhere (Koller *et al.* 2013). Assessing patients immediately pre-Tx, with follow-up at 6 months, 1 and 2 years post-Tx, the GERAS study began in January 2015 and will extend until June 2020. Figure 1 illustrates the study design, data sources and variables.

Study team and cooperation partners

This study is integrated in a research programme on ageing and frailty in KTx. Coordinated via the University of Basel's Institute of Nursing Science (INS), it represents a collaboration between five Swiss KTx centres, Johns Hopkins University (US), University of Pittsburgh (US) and the University of Lugano (Switzerland). Cooperation partners include the STCS, all participating hospitals' laboratories and management control units, the University Hospital Basel Clinical Trial Unit, Santésuisse and the Swiss *Krankenkasse* (healthcare fund).

Sample selection and size

A consecutive recruited convenience sample of adult deceased- and living-donor KTx recipients (aged ≥20 years) who are enrolled in the STCS is included, unless they are multiple organ Tx recipients, are incapable of informed consent (IC), have insufficient knowledge of English, French, German or Italian, or have severe functional impairments which could influence the cognitive tests. A power analysis for patient and graft survival (aim 1.1) indicated a minimum sample size of 250 patients for detection of proportional differences within reported ranges in both outcomes according to frailty status at KTx [5-year post-Tx patient survival: 77·5% for frail vs. 91·5% for non-frail patients, based on pre-KTx frailty prevalence (25·1% frail, 74·9% non-frail)], with 80% power and a two-sided alpha level of 0·05 (Garonzik-Wang *et al.* 2012, McAdams-Demarco *et al.* 2015b). Study enrolment began in February 2016 and will continue for approximately 25 months, guided by the yearly number of adult KTx in Switzerland ($n = 296$, data 2014) (SwissTransplant 2014) and 15% non-eligibility, 15% non-participation and 30% attrition.

Data sources, variables and measurements

Data sources include: (1) STCS datasets; (2) primary patient data collection via established or investigator-developed interview questionnaire (Table 1); and (3) other data sources (medical charts, hospitals' management control records, the Swiss healthcare fund, the Swiss Federal Statistical Office and the European Renal Association).

All GERAS study documents are available in English, French, German and Italian. They were developed via iterative processes with multiple review rounds by researchers. Culturally sensitive professional translations were performed. Thereafter, native-speaking research team members and nursing researchers reviewed translation accuracy, item comprehensibility and data availability at KTx centres. Using a convenience sample of haemodialysis patients, KTx candidates and KTx recipients, the procedures and instruments were pilot tested in three centres. Variables and measurements are described in detail below.

Primary variables of interest

Frailty is assessed pre-Tx, at 6 months, 1 year and 2 years posttransplant, using an adapted Fried Frailty Instrument (Table 2; Jha *et al.* 2016a). Originally developed and psychometrically tested in the US Cardiac Health Study (Fried *et al.* 2001), then modified for Tx patients, both the original and modified versions have good construct and predictive validity across chronically ill cohorts. In end-stage organ failure and Tx, it has predictive validity for biomedical outcomes in middle-aged and older adults (Garonzik-Wang *et al.* 2012, Hamaker *et al.* 2012, McAdams-Demarco *et al.* 2013b, 2015a,b, Lai *et al.* 2014b, Buta *et al.* 2015, Handforth *et al.* 2015, Theou *et al.* 2015). The modified version requires ten minutes to evaluate five domains: 'weakness' (measured hand grip strength), 'slowness' (measured habitual walking speed), 'a low level of physical activity' (one self-report item), 'a lower total energy expenditure' (one self-report item on subjective exhaustion) and 'chronic undernutrition' (one self-report item on loss of appetite). Given that pre- to posttransplant weight assessments often reflect fluctuating fluid levels, self-reported loss of appetite was used to measure chronic undernutrition. Summary scores indicate non-frailty (score 0), pre-frailty (score 1-2) or frailty (score 3-5) (Table 2) (Jha *et al.* 2016a).

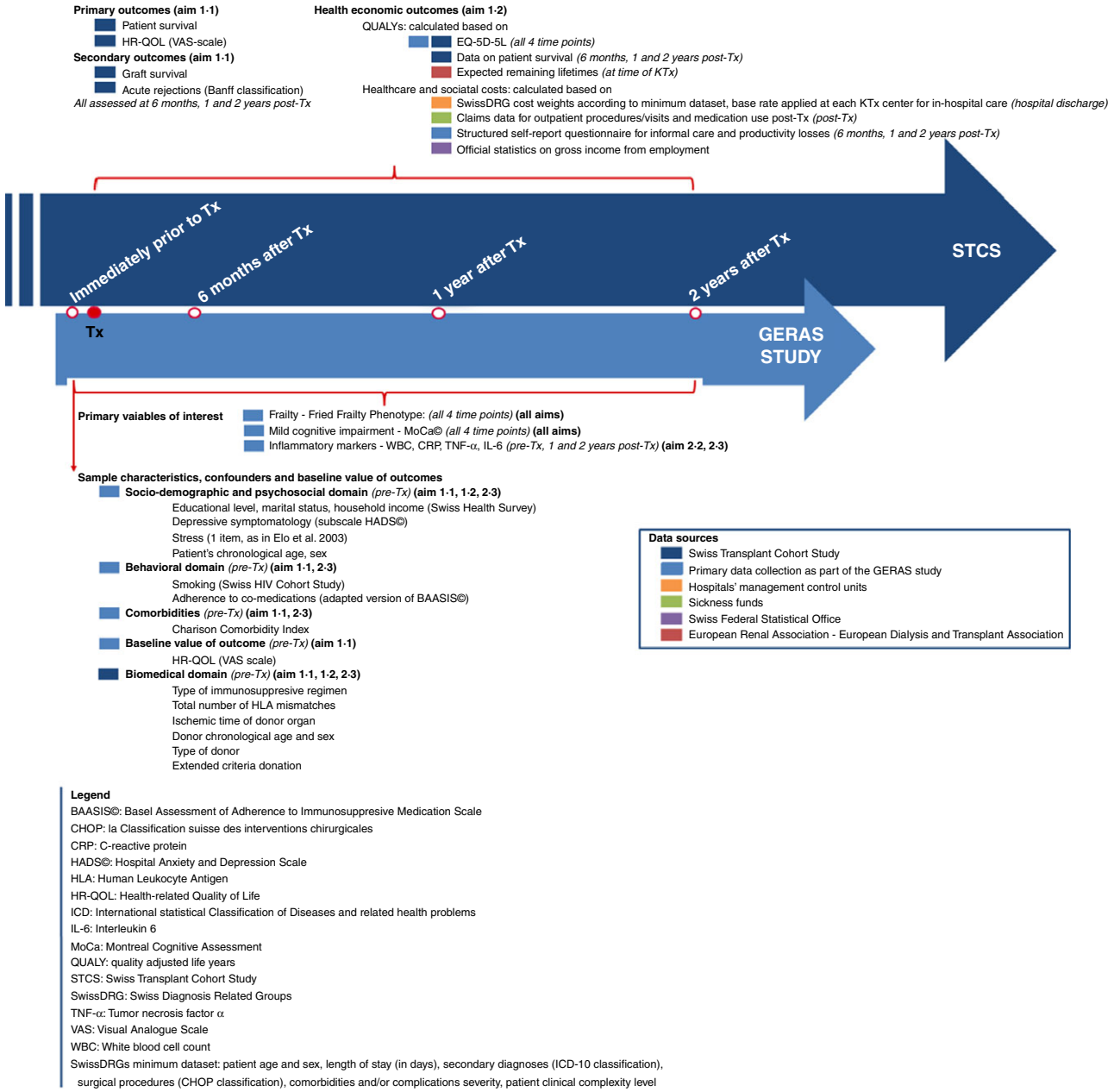

Figure 1 Flow chart of the GERAS study design, data sources and variables.

MCI is assessed via the Montreal Cognitive Assessment (MoCA) pre-Tx, then at 6 months, 1 year and 2 years post-Tx. This 10-minute assessment covers visiospatial and executive functioning, naming, memory, attention, language, abstraction, delayed recall and orientation (Nasreddine *et al.* 2005, Tiffin-Richards *et al.* 2014, Apostolo *et al.* 2015, Cecato *et al.* 2016, Julayanont *et al.* 2015). Regarding MCI detection in older community-dwelling adults and haemodialysis patients, the MoCA's sensitivity and specificity exceed those of the Mini Mental State Examination (gold standard). Possible scores range from 0-30; scores <26 indicate MCI. To avoid recall bias for certain items (e.g. general vocabulary, animal names, calculations), a different version is used for each measurement point (Nasreddine *et al.* 2005, Tiffin-Richards *et al.* 2014, Julayanont *et al.* 2015).

Inflammatory biomarkers: total WBC (in 10^9/L) and CRP (in milligrams per litre) are determined for venous blood samples (serum and ethylenediamine tetra-acetic acid sample) pre-Tx, then at 1 and 2 years post-Tx. As levels of TNF-α and IL-6 are not monitored in the STCS, measurements (in picograms per millilitre) are based on serum

Table 1 Investigator-developed questionnaire on informal care and productivity losses.

Construct	Instructions and question	Variable type and values
General information	Please fill out this general information before conducting the interview: a. Day of the interview b. Who was interviewed? c. Who conducted the interview?	a. Open-ended: Day/Month/Year b. Categorical: The patient / An informal caregiver of the patient / The patient and caregiver were interviewed together c. Open-ended: name and surname
Living arrangements of the patient	Where does the patient currently live?	Categorical: At home alone / At home with other people / In a healthcare or social organization (please indicate the name of the organization, and unit/ward – if applicable) / Other, please specify
Changes to the working condition of the patient	In the last 6 months / 1 year, did the patient have to change her/his working condition because of her/his kidney transplantation?	Categorical: No / She/he had to quit her/his job / She/he had to reduce the frequency of her/his occupation (please specify the reduction in %) / She/he lost working days (please specify how many days) / Other, please specify:
Homecare received	In the last 6 months / 1 year, did the patient and/or her/his relatives pay for homecare assistance because of the kidney transplantation?	Table indicating the following types of homecare assistance: domestic worker / companion / physiotherapist / nurse / other (please specify). For each, the interviewer indicates: a. Open-ended: Frequency with which the homecare assistance was received b. Open-ended: Total estimated expenditure by the patient and/or her/his relatives
Presence of and information on the patient's informal caregiver	a. Does the patient have a person who assists her/him in daily life, but is not paid for doing so (informal caregiver)? (Note: if the patient has more than one informal caregiver, please fill out this question for the person who assists her/him most frequently) b. What is the age of the informal caregiver? c. What is the sex of the informal caregiver? d. What is the working condition of the informal caregiver? e. If she/he is employed, please specify his/her function	a. Dichotomous: Yes / No (please stop the interview) b. Open-ended: years c. Dichotomous: Male / Female d. Categorical: Employed / Student / Housewife or – man / Retired / Unemployed e. Categorical: No management function / Top, upper or middle level management function / Lower management function / Other (please specify)
Presence of and information on the patient's informal caregiver (cont.)	a. Please specify the highest educational degree completed by the informal caregiver: b. What is the relationship of the informal caregiver with the patient?	a. Categorical: No completed school or professional education (less than 9 formation years) / Mandatory school (primary/secondary/junior high/district school) (9 formation years) / Apprenticeship or full-time vocational school (10-13 formation years) / Diploma qualifying for university admission (Matura) (13 formation years) / Higher professional education (e.g. master craftsman diploma, federal diploma) (14-16 formation years) / Higher technical or commercial school (e.g. school for social work, school for engineering) (14-18 formation years) / University degree (e.g. bachelor or master of science) (16 or more formation years) / Other education (open-ended question) / I do not want to answer b. Categorical: Spouse or partner / Son or daughter / Other family member (please specify) / Friend / Other (please specify)
Type of assistance provided by the informal caregiver	In the last 6 months / 1 year, which type(s) of assistance did the informal caregiver provide to the patient, and how much time did she/he dedicate for doing so?	Open-ended: table indicating 'type of assistance' and 'number of hours per day'

Table 1 (*Continued*).

Construct	Instructions and question	Variable type and values
Changes in the working condition of the informal caregiver	In the last 6 months / 1 year, did the informal caregiver have to change her/his working condition to assist the patient?	See item 'Changes to the working condition of the patient'
Financial support for informal caregiving	Does the informal caregiver receive financial support for assisting the patient?	Dichotomous: No / Yes (please specify the type and amount of financial support received)
Assistance provided to the patient by other people	a. In the last 6 months / 1 year, have there been other people who assisted the patient, although with less intensity than the caregiver? b. If yes, please fill out the following table	a. Dichotomous: No / Yes b. Open-ended: table indicating 'relationship with the patient' and 'number of hours per week'
Transportation expenditures for patient assistance incurred by the patient or the caregiver	a. In the last 6 months / 1 year, did the patient or the caregiver bear the burden of transportation expenditures for patient assistance? b. If yes, please fill out the following table, indicating information for a one-way trip (not a round-trip).	a. Dichotomous: No / Yes b. Open-ended: table indicating 'distance (km)', 'transportation means', 'estimated expenditure' and 'number of times'
Other expenditures for patient assistance incurred by the patient or the caregiver	a. In the last 6 months / 1 year, did the patient or the caregiver bear the burden of other expenditures for patient assistance? b. If yes, please fill out the following table, indicating the type, estimated cost and frequency of each expenditure.	a. Dichotomous: No / Yes b. Open-ended: table indicating 'type of expenditure', 'estimated expenditure' and 'number of times'

samples collected during the GERAS study. Each KTx centre's laboratory performs pre-analytical procedures according to study-specific standard operating procedures. The University Hospital Basel's Department of Laboratory Medicine coordinates shipping and analysis of the serum samples.

Primary, secondary and health economic outcomes

Primary outcomes for aim 1.1 are patient survival and HR-QOL; secondary outcomes are graft survival and acute rejection episodes. Health economic outcomes for aim 1.2 are QUALYs and health care and societal costs of KTx. Table 3 provides detailed information on all outcomes.

Socio-demographic variables

Three items are assessed pre-Tx using the STCS Psychosocial Questionnaire: educational level (categorical, nine answer categories), marital status (categorical, four answer options) and household income (categorical, five answer options). As noted above, the STCS self-report questionnaire consists of psychometrically tested items (De Geest *et al.* 2013, 2014). Patients' chronological age (continuous, in years) and sex (male / female) are retrieved via medical chart review.

Psychological and behavioural variables

Four psychosocial variables are assessed pre-Tx using the STCS Psychosocial Questionnaire: depressive symptomatology [Hospital Anxiety and Depression Scale-7 item depression subscale (Zigmond, 1983)], stress [categorical, five response options as in occupational research (Elo *et al.* 2003)], smoking (categorical, five answer options, from the Swiss HIV Cohort Study) and adherence to medications [two items on taking adherence and drug holidays from an adapted version of the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS©)] (Glass *et al.* 2006, 2008, Deschamps *et al.* 2008, Ducci *et al.* 2013, Marsicano Ede *et al.* 2013).

Biomedical variables

Five variables are extracted from STCS data: immunosuppressive regimen type (Azathioprine, Cyclosporin, EC-Mycophenolic acid, Everolimus, Glucocorticoid, Mycophenolat mofetil, Sirolimus, Tacrolimus, induction therapy), total number of HLA mismatches (count), cold ischaemic time of donor organ (minutes), donor and recipient chronological ages (years), donor and recipient sexes (male /female), donor type (post-brain death (DBD), post-circulatory death (DCD), living-related or living-unrelated), extended-criteria donor (yes /no). Information on the STCS data has previously been elaborated (Koller *et al.* 2013, De Geest *et al.* 2014). Based on medical chart review at KTx, the total number of comorbidities is assessed via a Charlson

Table 2 Fried Frailty Instrument as adapted for Tx patients (Fried *et al.* 2001).

Domain	Assessment and scoring
Weakness	*Assessment*: Grip strength as measured by the hand-held Jamar dynamometer (Sammons Preston Inc., Boiling Brook, IL), which has established test–retest, inter- and intra-rater reliability (Roberts *et al.* 2011). • Standardized assessment protocol from the American Society of Hand Therapy, as adapted by Roberts *et al.* (2011). • Mean values of three consecutive tests of maximum grip strength with the left and right hand are calculated. Grip strength is considered weak if this mean value is ≤ two standard deviations of sex- and age-adjusted normative values (Mathiowetz *et al.* 1985). • Hand dominance, and the location of a dialysis shunt are recorded. *Scoring*: 1 point if weakness is present.
Slowness	*Assessment*: Time in seconds to complete a 5 m walk at the patient's habitual pace is tested, measured following a standardized protocol. Walking speed is considered slow if the average of three attempts takes ≥6 seconds. *Scoring*: 1 point if slowness is present.
Low level of physical activity	*Assessment*: through 1 closed-ended question: 'How often do you engage in activities that require a low or moderate level of energy, such as gardening, cleaning the car or going for a walk? (Answer options: more than once a week / once a week / one to three times a month / hardly ever, or never). A response of 'one to three times a month' or 'hardly ever, or never' is classified as a low level of physical activity. *Scoring*: 1 point if a low level of physical activity is present.
Exhaustion	*Assessment*: through 2 closed-ended questions: 'In the last week, did you feel on at least three days, that everything you did was an effort?' and 'In the last week, did you feel on at least three days, that you could not get going?' (Answer option for each question: yes / no). A response of 'yes' to either one or both questions is considered as exhaustion. *Scoring*: 1 point if exhaustion is present.
Loss of appetite*	*Assessment*: through 1 closed-ended question: 'Have you, in the last three months, been eating more/ less than usual?' (Answer options: less / unchanged / more). A response of 'less' is classified as chronic undernutrition. *Scoring*: 1 point if chronic undernutrition is present.
Overall score	Non-frail: 0, Pre-frail: 1-2, Frail: 3-5

*The adaptation for Tx patients considers the item loss of appetite, which is questioned instead of unintentional weight loss. The latter is unreliable in Tx populations given potential fluid overload.

Comorbidity Index version adapted for KTx (Hemmelgarn *et al.* 2003). HR-QOL (VAS scale) will be measured pre-Tx to control for its baseline value.

Patient recruitment and data collection

Coordinated and led by the INS, patient recruitment and data collection involve four phases:

- *Training of data collectors*, including research team members, KTx centre nursing and medical staff and nursing science students. All are trained in their native language through personalized sessions at KTx centres. Moreover, each receives a step-by-step data collection manual and podcast and can contact GERAS team members if required.
- *Patient recruitment:* on patients' hospital admission for KTx, data collectors assess their eligibility and fulfil informed consent (IC) requirements for living- and deceased-donor grafts.
- *Data collection:* data collection packages are prepared at the INS and the coordinating laboratory. Patients' primary data are collected as follows: (1) patient data coding form, (2) Fried Frailty Instrument, (3) MoCA, (4) STCS Psychosocial Questionnaire, (5) venous blood sampling, (6) investigator-developed interview questionnaire on informal care received and productivity losses. Thereafter, the Charlson Comorbidity Index is scored based on medical chart review. Patient data collection booklets are stored in sealed envelopes and blood samples sent to participating laboratories according to centre-specific procedures.
- *Return of completed data collection booklets:* after storage in locked cabinets at the KTx centres,

Table 3 Overview of primary, secondary and health economic outcomes.

Outcome	Variable type and values Time point(s)	*Data source*, measurement and psychometrics (if applicable)
Patient survival (Primary outcome)	Dichotomous (yes / no) & time-to-event. 6 months, 1 and 2 years post-Tx.	STCS dataset: registered by two independent physicians. STCS Endpoint Committee ascertains registered deaths (Koller *et al.* 2013).
HR-QOL (Primary outcome)	Continuous (range 0-100). 6 months, 1 and 2 years post-Tx.	STCS dataset: VAS. Psychometric properties in oncology patients are reported in (de Boer *et al.* 2004).
Graft survival (Secondary outcome)	Dichotomous (yes / no) & time-to-event. 6 months, 1 and 2 years post-Tx.	STCS dataset: STCS classification developed by clinical experts (Koller *et al.* 2013).
Acute rejection (Secondary outcome)	Dichotomous (yes / no). 6 months, 1 and 2 years post-Tx.	STCS dataset: measured according to the Banff classification system (Wu *et al.* 2014, Wu *et al.* 2015).
Healthcare and societal costs (Health economic outcome)	Continuous, dichotomous & categorical. Pre-Tx, data reflecting time of hospital discharge, at 6 months, 1 and 2 years post-Tx.	Calculated based on: • Management control unit of KTx centres: SwissDRG cost weights associated to each patient case (in-hospital care) based on minimum dataset; base rate applied in each KTx centre (SwissDRG AG 2016). • Sickness funds [recruited through Santésuisse (Santésuisse, 2016)]: claims data for each outpatient procedure/visit performed or medication used (posttransplant). • Structured self-report questionnaire filled out by patients and/or their primary informal caregiver: informal care and productivity losses (see table 6). • Swiss Federal Statistical Office: Official statistics on gross income from employment to calculate cost of time (Swiss Federal Statistical Office 2014).
Quality-adjusted life years (QUALYs) (Health economic outcome)	Categorical, 5-point Likert scale. Pre-Tx, at 6 months, 1 and 2 years post-Tx. Dichotomous (yes / no) & time-to-event. 6 months, 1 and 2 years post-Tx. Continuous. At time of Tx.	Calculated based on: • Primary data collection with STCS Psychosocial questionnaire (pre-Tx, see 2.3.3.3); STCS dataset (posttransplant): EuroQol-5D-5L instrument (Drummond *et al.* 2015, EuroQol 2016). • STCS dataset: data on patient survival (see supra). • European Renal Association – European Dialysis and Transplant Association Registry: Annual Report for expected remaining lifetimes at time of KTx [European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), 2013].

KTx, kidney transplantation; Pre-Tx, pre-transplant; Post-Tx, post-transplant; STCS, Swiss Transplant Cohort Study; SwissDRG, Swiss Diagnosis Related Groups; Tx, transplantation; VAS, Visual Analogue Scale.

completed booklets are collected bi-monthly by research team members and confidentially stored at the INS data management centre. Prior to analysis, data quality (e.g. completeness) is verified.

Data management and analysis

In collaboration with the University Hospital Basel Clinical Trial Unit, a secure web-based data platform (SecuTrial®) is used to ensure comprehensive structured patient follow-up and to enter, manage, link and code data from all sources (SecuTrial, 2000). Initially, missing data, data distributions and violations of assumptions underlying applied statistical techniques are checked and handled as appropriate. All analyses employ STATA (StataCorp LP, College Station, TX, USA) and SAS (SAS Institute AG, Wallisellen, Switzerland) statistical software, applying a two-tailed significance level (α) of .05. Data analyses are performed as follows:

Aim 1.1: Patient survival (primary outcome) and graft survival (secondary outcome) require a competing risks analysis to account for simultaneous risks of mortality and graft loss in KTx (Pintilie 2007, Bakoyannis & Touloumi 2012, Koller *et al.* 2012, Wolbers *et al.* 2014, Geskus 2015). Standard analysis for this type of data results in overestimated outcome probabilities (Bakoyannis & Touloumi 2012, Wolbers *et al.* 2014, Fonseca *et al.* 2015, Geskus 2015). For both outcomes the cause-specific hazard

(CSH) and cumulative incidence functions (CIF) are displayed and a multivariate regression performed. Using frailty and MCI as independent variables of interest, socio-demographic, biomedical, psychosocial and behavioural variables are screened as potential confounders. Regression on the CSH consists of a Cox cause-specific proportional hazards model, regression on the CIF of a Fine and Gray model (Lee *et al.* 2012, Wolbers *et al.* 2014, Geskus 2015).

Aim 1.2: Regarding HR-QOL (primary outcome) and acute rejection episodes (secondary outcome), multivariate mixed effects logistic and linear regression models are applied to flexibly account for the multi-level clustered longitudinal data structure and missing data. In all models, patients are added as a random effect, with length of follow-up, frailty and MCI considered as fixed effects. Socio-demographic, biomedical, psychosocial and behavioural variables are tested as confounders. The necessity of including polynomials to model a non-linear relationship with HR-QOL is explored. In all models for aim 1.1, interaction between frailty and MCI is tested to explore a potential cumulative effect on outcomes. Also, the use of variable- or patient-clustering techniques is explored to summarize information on correlated variables. Model building applies a block-entry method.

Aim 1.3: For health economic outcomes, a discount rate of 3% is applied to both costs and QUALYs (Gold *et al.* 1996, Tan-Torres Edejer *et al.* 2003). Up to 2 years post-transplant, health care and societal costs and QUALYs are described via appropriate descriptive measures of central tendency and dispersion. Comparison of healthcare and societal costs, and QUALYs are performed for the three clinically relevant subgroups: non-frail vs. pre-frail/frail vs. pre-frail/frail with MCI. Graphic representations are applied for data visualization. A mixed effects log-linear regression model is applied for the continuous outcome variable of healthcare and societal costs, where patients are added as a random effect. Follow-up length, frailty, MCI and the interaction of the latter two conditions are considered fixed effects. Socio-demographic, biomedical and psychosocial variables are tested as confounders.

Aim 2.1: Prevalence, evolution and interrelationships between frailty and MCI are analysed descriptively from pre-Tx to 2 years posttransplant. Graphic methods are applied for data visualization. Changes over time are tested using mixed effects regression modelling, with frailty and MCI employed as mutual predictors to test for interrelationships between the two.

Aim 2.2: Descriptive statistics of central tendency and variability are applied to describe the levels of the selected inflammation markers (CRP, total WBC, TNF-α and IL-6) in relation to frailty status (non-frail, pre-frail or frail) and cognitive function (MCI, no MCI). Graphics are applied for data visualization. Associations between inflammatory markers, frailty and MCI are tested using a mixed effects (ordinal) logistic regression analysis, with frailty status (non-frail, pre-frail, frail) and MCI (yes/no) as outcome variables. Since inflammatory markers may be correlated, we explore the use of variable- or patient-clustering techniques.

Aim 2.3: The aetiological values of pre-Tx inflammatory markers regarding post-Tx changes in frailty status (non-frail, pre-frail, frail) are examined using mixed effects logistic regression models, entering patients as a random effect and follow-up time and inflammatory markers as fixed effects. To explore possible delayed effects of inflammatory marker information on frailty, we lag frailty status. Confounders and model building techniques are similar to those used for aim 1.1's mixed-effects models.

Regarding handling of missing data and sensitivity analyses, for all analyses, missing data's biasing effects are mapped and their influence on the modelling results explored using sensitivity analyses under various scenarios. For example, health economic evaluation (aim 1.2), sensitivity analyses use varying discount rates (0·0%, 5·0% and 6·0%) (Gold *et al.* 1996, Tan-Torres Edejer *et al.* 2003).

Ethical considerations

The STCS received ethical approval prior to data collection; its IC includes approval for further use of data in STCS approved studies such as this (De Geest *et al.* 2013, Koller *et al.* 2013). The GERAS study received ethical approval from all responsible ethical committees (Ref. Nr. EKNZ 2015-235). Participants will be provided with verbal and written information about the study. A written informed consent is obtained prior to participating in the study. Participation is voluntary and may be discontinued at any time without implications for patient treatment. We comply with all national and international guidelines and privacy laws concerning treatment of patients in clinical studies.

The GERAS study consortium

Patient and provider involvement is organized through an advisory body. Active partnerships are pursued between the research team, KTx patients, the Swiss Kidney Patient Association, KTx nursing, medical and allied health professionals, regional and national governing bodies and policy makers. Integrating these members' diverse perspectives will improve the study's quality, relevance and effectiveness

regarding researcher conduct and management, analysis, interpretation and dissemination of findings and monitoring and evaluation of the study process. Patient and provider involvement is also essential for successful implementation of our findings in KTx clinical practice and policy development and identification and prioritization of areas for further research (Involve Network and National Institute for Health Research, 2012, National Institute for Health Research and Research Design Service London, 2013).

Validity and reliability/Rigour

Several steps ensure the GERAS study's validity, reliability and rigour. Nesting the study in the rigourous longitudinal STCS data structure and the application of SecuTrial® for patient follow-up minimizes study drop-out and ultimate selection bias. Across all KTx centres, consistent use of methodologies proven in US and Australian studies on frailty and MCI (Jha *et al*. 2015, 2016a) ensures national and international comparability of results. Furthermore, all instruments have been tested for reliability and validity in previous studies including Tx populations. When the entire data collection procedure was pre-tested at three participating KTx centres, only minor adaptations were necessary. To check data quality, 5% of data booklets will be randomly tested, that is, two research team members will independently enter their contents for analysis.

Discussion

Clinical, scientific and policy impact

Accumulating evidence on the high prevalence and independent predictive values of frailty and MCI regarding inferior clinical outcomes features both as critical issues for solid organ Tx candidates and recipients. Only recently recognized in Tx, neither condition is fully considered in guidelines for Tx policy, patient assessment nor direct practice pathways. For the rapidly growing group of older Tx patients, GERAS findings on frailty and MCI will likely guide and optimize clinical management. This is particularly relevant in Swiss settings, where no upper age limit is applied to Tx candidacy. As the largest solid organ Tx group, KTx patients receive approximately 296 grafts in Switzerland yearly, each costing Swiss society between 60,000-100,000 Swiss Francs (Federal Office of Public Health, 2012). Thus, the GERAS study is addressing a significant challenge. Moving beyond previous biomedical-focused frailty research, it jointly examines frailty and MCI from bio-psychosocial and health economic perspectives. This study will continue to drive improvements in care quality and appropriateness and of policy development for ageing and frail KTx cohort as follows:

- Through its comprehensive perspective, the GERAS study will significantly enhance risk prediction regarding adverse outcomes in KTx. Integrating its findings in clinical practice guidelines and training programs will guide modifications in the complex care of pre-frail and frail patients. In addition to enhancing therapeutic decision-making concerning transplant candidacy, it may even accelerate and improve posttransplant rehabilitation and related outcomes (e.g. via enhanced physical therapy, exercise and nutrition). As such an approach is patient-centred, nurses will be key participants, helping optimize chronic illness and symptom management while providing evidence-based psychosocial support.
- Nested in the STCS, studying a nationally representative cohort of KTx patients including older recipients, GERAS enables rigourous study of the clinical, psychosocial and health economic consequences of kidney Tx in frail and/or cognitively impaired patients.
- Given the expansion of Tx eligibility to older and more vulnerable patients, it is imperative to understand the impact of frailty and MCI on KTx's cost-effectiveness. Considering patient, healthcare system and societal perspectives, GERAS will identify the risks of transplanting frail and/or MCI patients. At the policy level, it will provide essential evidence about the optimal use of limited resources to maximize health outcomes in adults with ESRD.
- Investigating inflammatory biomarkers in KTx will provide preliminary insights into the relevance of chronic low-grade systemic inflammation as a pathway to frailty and MCI. By exploring these biomarkers' values, GERAS will notably contribute to scientific advancements in pre-KTx screening for frailty and MCI. Supporting diagnosis of both will facilitate tracking their development and assist healthcare professionals in clinical and therapeutic decision-making.

Strengths and limitations

The GERAS project has three key strengths. First, its multicentre design and nationally representative cohort considerably expand current evidence on frailty and MCI in KTx, with generalizable results. Second, by jointly examining frailty and MCI from a comprehensive bio-psychosocial

and health economic perspective, it significantly broadens the existing–primarily clinical–research focus. Third, competing risks analysis is a pioneering methodology: despite the frequent occurrence of competing outcomes, the use of this statistical technique in Tx is still in its infancy (Huang *et al.* 2014, Aubert *et al.* 2015, Fonseca *et al.* 2015, Sapir-Pichhadze *et al.* 2016).

Conversely, certain limitations should be considered when interpreting our findings. Balanced against our power analysis's required sample size, the rather small number of KTx performed annually in Switzerland precludes a randomized sampling strategy to enhance generalization. Finally, Switzerland's small population, linguistic diversity, variability across care systems and KTx centres and heterogeneous clinical profiles of KTx donors and recipients might diffuse the impact of frailty and MCI on outcomes.

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Conflict of interest

No conflict of interest has been declared by the author(s).

Author contributions

All authors have agreed on the final version of the paper and meet at least one of the following criteria [recommended by the International Committee of Medical Journal Editors (ICMJE) (http://www.icmje.org/ethical_1author.html)]:

- substantial contributions to conception and design, acquisition of data or analysis and interpretation of data.
- drafting the article or revising it critically for important intellectual content.

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Appendix

GERAS Study Consortium Members

Kidney transplant patients, the Swiss Kidney Patient Association, nursing, medical and allied health professionals, regional and national governing bodies and policy makers.

Psychosocial Interest Group of the STCS

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